CLAIMS

What Is Claimed Is:

1. A process for preparing amorphous fexofenadine hydrochloride comprising the steps of:
   a) preparing a solution of fexofenadine hydrochloride in THF;
   b) removing a portion of THF from the solution;
   c) adding a C_5 to a C_{12} saturated hydrocarbon to the remaining THF to form an upper and a lower layer, wherein the lower layer is oily;
   d) separating the upper layer from the lower layer; and
   e. drying the lower layer to obtain amorphous fexofenadine hydrochloride.
2. The process of claim 1, wherein the saturated hydrocarbon is cyclohexane.
3. The process of claim 1, wherein the volume of THF after removal is negligible compared to the volume of the less polar organic solvent.
4. The process of claim 1, wherein THF is removed by evaporation.
5. The process of claim 1, wherein the lower layer is dried by evaporation.
6. A process for preparing amorphous fexofenadine hydrochloride comprising:
   a) preparing a solution of fexofenadine hydrochloride in an organic solvent; and
   b) reomoving the solvent to obtain amorphous fexofenadine hydrochloride.
7. The process of claim 6, wherein the organic solvent is selected from the group consisting of an ester, ether, alcohol and ketone.
8. The process of claim 7, wherein the alcohol is selected from the group consisting of methanol, ethanol and isopropanol.
9. The process of claim 6, wherein the ketone is acetone.
10. The process of claim 6, wherein the solvent is removed by evaporation.
11. Fexofenadine hydrochloride Form V.

12. Fexofenadine hydrochloride of claim 11 chracterized by a water content of from about 30 to about 56%.

13. Fexofenadine hydrochloride having a PXRD pattern with peaks at about 15.9, 16.8, 17.2, 20.9, 21.5, 21.8 ±0.2 degrees two theta.

14. The fexofenadine hydrochloride of claim 13, having a PXRD pattern with peaks at about 7.2, 7.9, 8.6, 11.0, 13.7, 14.8, 15.6, 16.9, 17.2, 17.9, 18.4, 18.7, 19.9, 20.4, 20.9, 21.2, 21.5, 21.8, 22.1, 23.1, 23.8, 24.6, 25.4 ±0.2 degrees two theta.

15. The fexofenadine hydrochloride Form V of claim 14 that produces a PXRD pattern substantially as depicted in Fig. 1.

16. A process for preparing fexofenadine hydrochloride Form V comprising the steps of:

    a) preparing a solution of fexofenadine hydrochloride in a mixture of water and an alcohol selected from the group consisting of methanol, isopropanol, ethanol and 1-butanol;

    b) precipitating fexofenadine hydrochloride from the solution; and

    c) separating the precipitate.

17. The process of claim 16, wherein the mixture has a ratio of about 2:1 of water to alcohol.

18. Fexofenadine hydrochloride Form VI.

19. Fexofenadine hydrochloride having a PXRD pattern with peaks at about 15.7, 16.1, 17.0, 17.3, 18.6, 18.8±0.2 degrees two theta.

20. The fexofenadine hydrochloride of claim 19 that produces a PXRD pattern with peaks at about 7.2, 7.9, 8.6, 11.0, 11.3, 13.3, 13.7, 14.8, 15.6, 15.9, 16.1, 16.9, 17.0, 17.2, 17.3, 17.9, 18.4, 18.6, 18.7, 19.9, 20.4, 20.9, 21.2, 21.5, 21.8, 22.1, 23.1, 23.8, 24.6, 25.4, 26.8, 27.7, 28.7, 29.7 ±0.2 degrees two theta.

21. The fexofenadine hydrochloride of claim 20 that produces a PXRD pattern substantially as depicted in Fig. 2.

22. A process for preparing fexofenadine hydrochloride Form VI comprising the steps of:

a) preparing a solution of fexofenadine hydrochloride in a mixture of water and 1-propanol;

b) precipitating fexofenadine hydrochloride from the solution; and

c) separating the precipitate.

23. The process of claim 22, wherein the mixture is from about a 2:1 to about a 4:1 mixture of water and 1-propanol.

24. A process for preparing fexofenadine hydrochloride Form VI comprising the steps of:

a) preparing a solution of fexofenadine hydrochloride in THF;

b) adding water to the solution to form a precipitate; and

c) separating the precipitate.

25. A process for preparing fexofenadine hydrochloride Form II comprising heating fexofenadine hydrochloride selected from the group consisting of Form V and Form VI to a temperature of from about 40°C to about 80°C.

26. The process of claim 25, wherein the temperature is about 40°C.

27. Fexofenadine hydrochloride Form VIII.

28. Fexofenadine hydrochloride having a PXRD pattern with peaks at 8.5, 11.0, 11.4, 13.4, 13.8, 17.1, 20.0, 21.5±0.2 degrees two theta.

29. The fexofenadine hydrochloride of claim 28 having a PXRD pattern substantially as depicted in Fig. 3.

30. Fexofenadine hydrochloride having a DSC thermogram with endothermic peaks at about 84°C and about 142°C.

31. Fexofenadine hydrochloride having a DTG profile as depicted in Fig. 5.

32. A process for preparing fexofenadine hydrochloride Form VIII comprising the steps of:

a) preparing a solution of fexofenadine free base in a basic aqueous solvent;

b) adding hydrochloric acid to the solution to form a precipitate; and

c) separating the precipitate.

33. The process of claim 32, further comprising a step of drying the precipitate.

34. Fexofendine hydrochloride Form IX.

35. Fexofenadine hydrochloride characterized by a PXRD pattern with peaks at about 4.7, 9.3, 17.4, 18.2, 19.4, 19.6, 21.6 and 24.0±0.2 degrees two theta.

36. The fexofenadine hydrochloride of claim 35 having a PXRD pattern substantially as depicted in Fig. 6.

37. Fexofenadine hydrochloride characterized by a differential scanning calorimetry endothermic peak at about 139°C.

38. A process for preparing fexofenadine hydrochloride Form IX comprising the steps of:

    a) preparing a solution of fexofenadine hydrochloride in acetone;

    b) adding the solution to an anti-solvent to form a precipitate; and

    c) separating the precipitate.

39. The process of claim 38, further comprising drying the precipitate.

40. The process of claim 38, wherein the anti-solvent is an ether.

41. The process of claim 40, wherein the ether is MTBE.

42. The process of claim 38, wherein the anti-solvent is a C_5-C_{12} saturated hydrocarbon.

43. The process of claim 42, wherein the saturated hydrocarbon is cyclohexane.

44. Fexofenadine hydrochloride MTBE solvate.

45. Fexofenadine hydrochloride MTBE solvate of claim 44 characterized by a DTG profile with endotherms at about 100°C and about 125°C.

46. A process for preparing fexofenadine hydrochloride MTBE solvate comprising the steps of:

    a) adding fexofenadine hydrochloride Form IX to MTBE to form the solvate; and

    b) separating the solvate.

47. Fexofenadine hydrochloride cyclohexane solvate.

48. The solvate of claim 47 characterized by a DTG profile with endotherms at about 99°C to about 110°C and about 140°C to about 150°C.

49. A process for preparing fexofenadine hydrochloride cyclohexane solvate comprising the steps of:

a) adding fexofenadine hydrochloride Form IX to cyclohexane to form the solvate; and

b) separating the solvate.

50. Fexofenadine hydrochloride Form X.

51. The fexofenadine hydrochloride of claim 50 having a water content of about 7.5 to 8.5%.

52. Fexofenadine hydrochloride having a PXRD pattern with peaks at about 4.2, 8.0, 9.3, 14.2, 16.0, 16.8, 17.6, 18.8, 20.0, 20.6, 21.7, 22.9, 23.8, 24.2 and 25.4 ± 0.2 degrees two theta.

53. The fexofenadine hydrochloride of claim 52 having a PXRD pattern substantially as depicted in Fig. 9.

54. Fexofenadine hydrochloride characterized by a DTG profile with a maximum endotherm at about 100°C and a minor endotherm at about 138°C.

55. A process for preparing fexofenadine hydrochloride Form X comprising the steps of:

a) preparing a solution of fexofenadine hydrochloride in methanol, and optionally adding dichloromethane to said solution;

b) adding a C_5 to a C_{12} saturated hydrocarbon to the solution to form a precipitate; and

c) separating the precipitate.

56. The process of claim 55, further comprising drying the precipitate.

57. The process of claim 55, wherein the saturated hydrocarbon is selected from the group consisting of cyclohexane and heptane.

58. The process of claim 55, further comprising a step of drying the precipitate.

59. A process for preparing fexofenadine hydrochloride Form X comprising the steps of:

a) preparing a solution of fexofenadine hydrochloride in methanol;

b) removing methanol to obtain a residue;

c) adding a mixture of methanol and an anti-solvent to the residue to form a precipitate; and

d) separating the precipitate.

60. The process of claim 59, wherein the anti-solvent is a monoaromatic hydrocarbon.

61. The process of claim 60, wherein the monoaromatic hydrocarbon is selected from the group consisting of toluene and xylene.

62. The process of claim 59, wherein the anti-solvent is a C_5 to a C_{12} saturated hydrocarbon.

63. The process of claim 62, wherein the anti-solvent is heptane.

64. The process of claim 59, further comprising drying the precipitate.

65. Fexofenadine hydrochloride Form XI.

66. Fexofenadine hydrochloride having a PXRD pattern with peaks at about 8.7, 14.5, 14.9, 16.6, 17.2, 18.3, 19.5, 21.2, 22.1 and 23.3 ± 0.2 degrees two theta.

67. The fexofenadine hydrochloride of claim 66 having a PXRD pattern substantially as depicted in Fig. 10.

68. A process for preparing fexofenadine hydrochloride Form XI comprising the steps of:

a) preparing a solution of fexofenadine hydrochloride in methanol;

b) adding the solution to toluene to form a precipitate; and

c) separating the precipitate.

69. The process of claim 68, further comprising drying the precipitate.

70. Fexofenadine hydrochloride Form XII.

71. Fexofenadine hydrochloride that produces a PXRD pattern with peaks at about 5.2, 7.9, 8.1, 12.1, 18.5, 19.0 ± 0.2 degrees two theta.

72. The fexofenadine hydrochloride of claim 71 wherein the PXRD pattern has peaks at about 5.2, 7.9, 8.1, 12.1, 13.3, 14.4, 14.7, 16.6, 18.5, 19.0, 19.5, 19.8, 21.7, 22.1, 24.2, 24.6, 26.7 ± 0.2 degrees two theta.

73. The fexofenadine hydrochloride of claim 72 characterized by a PXRD pattern substantially as depicted in Fig. 11.

74. Fexofenadine hydrochloride characterized by a FTIR spectrum with peaks at about 731, 845, 963, 986, 999, 1072, 1301, 1412 and 3313 cm^{-1}.

75. The fexofenadine hydrochloride of claim 74 further characterized by a FTIR spectrum with peaks at about 581, 640, 705, 748, 1165, 1337, 1367, 1448, 1468, 1700, 2679, 2934 and 3312 cm^{-1}.

76. The fexofenadine hydrochloride of claim 75 characterized by a FTIR spectrum substantially as depicted in Fig. 12.

77. A process for preparing fexofenadine hydrochloride Form XII comprising the steps of:

    a) preparing a solution of fexofenadine hydrochloride in ethanol;

    b) removing ethanol to obtain a residue;

    c) adding a mixture of ethanol and toluene to the residue to form a precipitate; and

    d) separating the precipitate.

78. The process of claim 77, wherein ethanol is removed by evaporation.

79. The process of claim 77, wherein the mixture has a ratio of about 8:1 to about 16:1 of toluene to ethanol.

80. The process of claim 77, further comprising drying the precipitate.

81. Fexofenadine hydrochloride Form XIII.

82. Fexofenadine hydrochloride characterized by a PXRD pattern with peaks at about 5.5, 6.8, 16.0, 16.3 ± 0.2 degrees two theta.

83. The fexofenadine hydrochloride of claim 82 wherein the PXRD pattern has peaks at about 5.5, 6.8, 10.7, 11.0, 13.6, 14.2, 14.9, 16.0, 16.3, 18.1, 18.9, 19.5, 20.6, 21.5, 22.0, 23.4, 24.2, 24.9, 26.0 ± 0.2 degrees two theta.

84. The fexofenadine hydrochloride of claim 83 characterized by a PXRD pattern substantially as depicted in Fig. 13.

85. Fexofenadine hydrochloride characterized by a DSC thermogram with an endothermic peak at about 185-195°C.

86. Fexofenadine hydrochloride characterized by a FTIR spectrum with peaks at about 1249, 1365, 1719 and 3366cm^{-1}.

87. The fexofenadine hydrochloride of claim 86 having a FTIR spectrum with peaks at about 639, 705, 746, 855, 963, 995, 1069, 1159, 1249, 1365, 1449, 1474, 1719, 2653, 2681, 2949, 3067, 3261 and 3366cm^{-1}.

88. The fexofenadine hydrochloride of claim 87 characterized by a FTIR spectrum as substantially depicted in Fig. 15.

89. A process for preparing fexofenadine hydrochloride Form XIII by heating fexofenadine hydrochloride Form XII for a sufficient amount of time to obtain Form XIII.

90. The process of claim 89, wherein fexofenadine hydrochloride Form XII is heated to a temperature of at least about 80°C.

91. The process of claim 89, wherein the process is stopped before complete transformation to fexofenadine hydrochloride Form XIII to obtain a mixture of Form XII and Form XIII.

92. A fexofenadine hydrochloride ethyl acetate solvate.

93. Fexofenadine hydrochloride ethyl acetate solvate Form XIV.

94. Fexofenadine hydrochloride ethyl acetate solvate characterized by a PXRD diffraction pattern with peaks at about 5.4, 5.7, 10.9, 11.4, 11.6 ± 0.2 degrees two theta.

95. The fexofenadine hydrochloride ethyl acetate solvate of claim 94 characterized by a PXRD pattern substantially as depicted in Fig. 16.

96. Fexofenadine hydrochloride ethyl acetate solvate characterized by a DSC thermogram with an endothermic peak at about 100°C.

97. Fexofenadine hydrochloride ethyl acetate solvate characterized by a FTIR spectrum with peaks at about 634.3, 699.5, 1335, 1359 and 1725 cm^{-1}, wherein the peaks at 1335, 1359 and 1725 are split.

98. The fexofenadine hydrochloride ethyl acetate solvate of claim 97 having a FTIR spectrum substantially as depicted in Fig. 20.

99. A process for preparing fexofenadine hydrochloride ethyl acetate solvate Form XIV comprising:

a) dissolving fexofenadine hydrochloride in methanol;

b) removing methanol to obtain a residue;

c) adding a mixture of methanol and toluene to the residue to form a precipitate;

d) separating the precipitate;

e) adding the precipitate to ethyl acetate to form the solvate; and

f) separating the solvate.

100. The process of claim 99, wherein methanol is removed by evaporation.

101. The process of claim 99, further comprising a step of drying the solvate.

102. The process of claim 99, wherein the ratio of the mixture is about 8:1 to about 14:1 of toluene to methanol.

103. A process for preparing fexofenadine hydrochloride ethyl acetate solvate Form XIV comprising triturating fexofenadine hydrochloride From X in ethyl acetate.

104. Fexofenadine hydrochloride ethyl acetate solvate Form XV.

105. Fexofenadine hydrochloride characterized by a PXRD pattern with peaks at about 5.5, 5.8, 16.4, 16.9, 18.4 ± 0.2 degrees two theta.

106. The fexofenadine hydrochloride of claim 105 having a PXRD pattern substantially as depicted in Fig. 18.

107. Fexofenadine hydrochloride characterized by a DSC thermogram with an endotherm at about 140°C.

108. Fexofenadine hydrochloride ethyl acetate solvate characterized by a FTIR spectrum as substantially depicted in Fig. 21.

109. A process for preparing fexofenadine hydrochloride ethyl acetate solvate Form XV comprising the steps of:

a) dissolving fexofenadine hydrochloride in ethanol;

b) removing ethanol to obtain a residue;

c) adding a mixture of toluene and ethanol to the residue to form a precipitate;

d) separating the precipitate;

e) adding the precipitate to ethyl acetate to form the solvate; and

f) separating the solvate.

110. The process of claim 109, wherein ethanol is removed by evaporation.

111. The process of claim 109, further comprising drying the solvate.

112. The process of claim 109, wherein the mixture has a ratio of 8:1 to 14:1 of toluene to ethanol.

113. A process for preparing fexofenadine hydrochloride Form XV comprising triturating fexofenadine hydrochloride Form XII in ethyl acetate.

114. A pharmaceutical composition comprising:

a) fexofenadine hydrochloride selected from the group consisting of Form V, Form VI, Form VIII, Form IX, Form IX-MTBE solvate, Form IX-cyclohexane solvate, Form X, Form XI, Form XII, Form XIII, Form XIV and Form XV; and

b) a pharmaceutically acceptable excipient.

115. A pharmaceutical dosage form comprising the pharmaceutical composition of claim 114.

116. The pharmaceutical dosage form of claim 115, wherein the dosage form is a capsule or tablet.

117. A unit dosage of the pharmaceutical dosage form of claim 115 containing about 30 to about 180 mg of fexofenadine hydrochloride.

118. A method of inhibiting binding between an H_1 receptor and histamine in a mammal comprising administering the pharmaceutical composition of claim 114 to the mammal.

119. The method of claim 118, wherein the mammal has symptoms selected from the group consisting of contraction of the bronchi, vasodilation, excessive mucus as result of inflammation and itching.

120. A method of alleviating symptoms of allergic rhinitis in a patient susceptible to allergic rhinitis or experiencing symptoms of allergic rhinitis comprising administering to the patient the pharmaceutical composition of claim 114.